Osteoradionecrosis of the Mandible

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Abstract: Background and Purpose:: Osteoradionecrosis (ON) of the mandible is a serious late complication of high-dose radiation therapy for tumors of the oropharynx and oral cavity. After doses between 60 and 72 Gy using standard fractionation, an incidence of ON between 5% and 15% is reported in a review from 1989, whereas in more recent publications using moderately accelerated or hyperfractionated irradiation and doses between 69 and 81 Gy, the incidence of ON is between < 1% and 6%. Intensity-modulated radiation therapy (IMRT) is expected to translate into a further important reduction of ON. The aim of this descriptive study was to assess absolute and relative bone volumes exposed to high IMRT doses, related to observed bone tolerance. Patients and Methods:: Between December 2001 and November 2004, 73 of 123 patients treated with IMRT were identified as subgroup "at risk" for ON (> 60 Gy for oropharyngeal or oral cavity cancer). 21/73 patients were treated in a postoperative setting, 52 patients underwent primary definitive irradiation. In 56 patients concomitant cisplatin-based chemotherapy was applied. Mean follow-up time was 22 months (12-46 months). Oral cavity including the mandible bone outside the planning target volume was contoured and dose-volume constraints were defined in order to spare bone tissue. Dose-volume histograms were obtained from contoured mandible in each patient and were analyzed and related to clinical mandible bone tolerance. Results:: Using IMRT with doses between 60 and 75 Gy (mean 67 Gy), on average 7.8, 4.8, 0.9, and 0.3 cm3 were exposed to doses > 60, 65, 70, and 75 Gy, respectively. These values are substantially lower than when using three-dimensional conformal radiotherapy. The difference has been approximately quantified by comparison with a historic series. Additional ON risk factors of the patients were also analyzed. Only one grade 3 ON of the lingual horizontal branch, treated with lingual decortication, was observed. Conclusion:: Using IMRT, only very small partial volumes of the mandibular bone are exposed to high radiation doses. This is expected to translate into a further reduction of ON and improved osseointegration of dental implants

DOI: https://doi.org/10.1007/s00066-006-1477-0

Osteoradionecrosis of the Mandible

Minimized Risk Profile Following Intensity-Modulated Radiation Therapy (IMRT)

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Background and Purpose: Osteoradionecrosis (ON) of the mandible is a serious late complication of high-dose radiation therapy for tumors of the oropharynx and oral cavity. After doses between 60 and 72 Gy using standard fractionation, an incidence of ON between 5% and 15% is reported in a review from 1989, whereas in more recent publications using moderately accelerated or hyperfractionated irradiation and doses between 69 and 81 Gy, the incidence of ON is between < 1% and ~ 6%. Intensity-modulated radiation therapy (IMRT) is expected to translate into a further important reduction of ON. The aim of this descriptive study was to assess absolute and relative bone volumes exposed to high IMRT doses, related to observed bone tolerance.
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Results: Using IMRT with doses between 60 and 75 Gy (mean 67 Gy), on average 7.8, 4.8, 0.9, and 0.3 cm^3 were exposed to doses > 60, 65, 70, and 75 Gy, respectively. These values are substantially lower than when using three-dimensional conformal radiotherapy. The difference has been approximately quantified by comparison with a historic series. Additional ON risk factors of the patients were also analyzed. Only one grade 3 ON of the lingual horizontal branch, treated with lingual decortication, was observed.
Conclusion: Using IMRT, only very small partial volumes of the mandibular bone are exposed to high radiation doses. This is expected to translate into a further reduction of ON and improved osseointegration of dental implants.

Key Words: Osteoradionecrosis · IMRT · Normal-tissue tolerance · Mandible bone · Dental implants

Strahlenther Onkol 2006;182:283–8
DOI 10.1007/s00066-006-1477-0

Osteoradionekrose der Mandibula. Geringeres Risiko durch intensitätsmodulierte Radiotherapie (IMRT)

Hintergrund und Ziel: Die Osteoradionekrose (ON) des Unterkiefers ist eine schwerwiegende Komplikation kurativer normofraktionierter Radiotherapie von Oropharynx- und Mundhöhlenkarzinomen. Nach Dosen zwischen 60 und 72 Gy besteht gemäß den Angaben einer Übersicht aus dem Jahr 1989 eine ON-Inzidenz von 5–15%, während laut neueren Arbeiten über leicht akzelerierte oder hyperfraktionierte Behandlungsschemata mit Dosen von 69–81 Gy die ON-Inzidenz zwischen < 1% und ca. 6% beträgt. Intensitätsmodulierte Radiotherapie (IMRT) dürfte die ON-Rate weiter reduzieren. Ziel dieser deskriptiven Arbeit war, absolute und relative Knochenvolumina mit hoher Dosisexposition zu evaluieren und in Beziehung zur beobachteten Knochentoleranz der eigenen Patienten nach IMRT-Behandlung zu setzen.
Patienten und Methodik: Zwischen Dezember 2001 und November 2004 wurden an der eigenen Klinik 123 Patienten mit Tumoren der Kopf-Hals-Region mit IMRT behandelt; hiervon waren 73 einer Untergruppe von Patienten mit Risiko für ON zuzurechnen (Karzinome des Oropharynx oder der Mundhöhle und Herddosen > 60 Gy). 21 Patienten wurden postoperativ, 52 primär kurativ bestrahlt; 56 erhielten eine simultane cisplatinbasierte Chemotherapie. Die mittlere Beobachtungszeit betrug 22 Monate (12–46 Monate). Die Mundhöhle inkl. Kieferknochen außerhalb des Planungszielvolumens wurde konturiert, und Dosis-Volumen-Bedingungen zur Organschonung wurden festgelegt. Retrospektiv wurde für jeden Patienten das gesamte Kieferknochenvolumen konturiert, und die Dosis-Volumen-Histogramme wurden im Hinblick auf die klinische Knochentoleranz ausgewertet.
Ergebnisse: Durch IMRT in Dosen zwischen 60 und 75 Gy (Mittelwert 67 Gy) wurden im Mittel 7,8, 4,8, 0,9 und 0,3 cm^3 einer Dosis von > 60, 65, 70 und 75 Gy ausgesetzt (Tabelle 1 und Abbildung 1). Diese Werte sind deutlich kleiner als nach konventio-

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Received: June 22, 2005; accepted: December 15, 2005

neller Bestrahlung. Der Unterschied wurde im Vergleich mit einer historischen Serie näherungsweise quantifiziert (Abbildung 3). Zusätzliche Risikofaktoren der eigenen Patienten wurden analysiert (Abbildung 2). Nur ein ON-Ereignis (Grad 3) im Bereich des lingualen Horizontalasts der Mandibula wurde beobachtet und erfolgreich mit einer lingualen Dekortikation behandelt.
Schlussfolgerung: Mittels IMRT werden nur sehr kleine Knochenvolumina hohen Bestrahlungsdosen ausgesetzt. Durch diese Knochenschonung werden eine weitere Reduktion des ON-Risikos und eine höhere Erfolgsrate rekonstruktiver Zahnimplantate (Tabelle 2) erwartet.

Schlüsselwörter: Osteoradionekrose · IMRT · Normalgewebstoleranz · Kieferknochen · Zahnimplantate

Introduction

Delivering high doses (> 60 Gy) with moderately accelerated or hyperfractionated schedules with three-dimensional conformal radiotherapy (3D-CRT) techniques, as in use since about 1990, the incidence of osteoradionecrosis (ON) could be reduced from approximately 15% to about 5% [1].

In several large prospective studies on fractionation regimens or combined chemoradiation studies using 3D-CRT since about 1990 in patients with carcinoma of the oropharynx or oral cavity, an incidence of ON between < 1% and approximately 6% has been observed [19, 20]. In our patients receiving hyperfractionated radiotherapy to a total dose between 72 and 76.8 Gy, incidence of ON was 20.1% (51% if there were teeth in the irradiated bone). An increased ON risk has been described when more than half of the horizontal branch of the mandible is exposed to high doses [7]. In a more recent analysis that included hyperfractionated and accelerated 3D-CRT schedules until 2002 [19], a correlation with exposed bone volume was not clearly evident, probably due to the small sample size of events. According to Emami et al. [5] the dose for a risk of 5% in 5 years (TD5/5) is 65 or 60 Gy if one third or at least two thirds of the mandible are exposed, whereas the TD50/5 is 77 or 72 Gy if one third or at least two thirds of the mandible are exposed.

Cisplatin- and 5-fluorouracil-based chemotherapy is not reported to influence the ON risk.

Using intensity-modulated radiotherapy (IMRT), dose-volume relationships are expected to substantially improve in favor of the mandible bone, while a similar or better target coverage is achieved compared to 3D-CRT. Using dose-volume constraints for mandible bone-sparing purposes, doses to the mandible, as well as mandible bone volumes exposed to relevant doses are hypothesized to be reducible to a non-critical value in all patients except those with bone-infiltrating tumors or large tumors close to the bone.

Early experiences in IMRT with respect to mandible bone tolerance are presented.

Patients and Methods

Patients

Out of 123 head-and-neck cancer patients undergoing IMRT between December 2001 and November 2004, a subgroup of 73 patients "at risk" for ON has been analyzed. Mean follow-up time was 22 months (range 12–46 months). Based on our past experience [19], we considered the following patients "at risk" of developing ON following radiation therapy: patients with primary tumor of the oral cavity (n = 18) or oropharynx (n = 55) who completed their IMRT course to a prescribed total dose (PTD) of at least 60 Gy (n = 2; 64 patients ≥ 66 Gy). In our previous series, no ON events were observed in irradiated nasopharyngeal and hypopharyngeal cancer patients [7, 19]. Additional potential risk cofactors were assessed (tumor invasion into the mandible bone, tumor close to bone, entire bone diameter exposed to ≥ 95% of PTD, bone volume exposed to doses > 70 Gy, teeth in high-dose bone areas).

IMRT was delivered using simultaneously integrated boost technique (SIB-IMRT). 52 of the 73 patients underwent primary definitive irradiation, the remaining 21 were treated in a postoperative setting. 37/73 patients (50%) presented with a locally advanced stage T3/4. In five cases with a T1/2 primary, extensive nodal disease (N2c) was diagnosed. Six patients were treated for recurrent disease. The remaining 25 patients suffered from an early-stage tumor (T1–2 N0–2b). Gender ratio was 1 : 4 in favor of men (14 women vs. 59 men), mean age was 60.2 years (41–85 years). In 56 patients (77%) concomitant cisplatin-based chemotherapy was applied. In the majority of patients, a positron emission tomography (PET) was available for radiation treatment planning [10]. All patients were regularly followed in collaboration with surgeons of our head-and-neck surgery or maxillofacial surgery joint clinics. Follow-up intervals were 2 and 6 weeks after IMRT completion, then every 2–3 months. Toxicity assessments were performed using the EORTC/RTOG toxicity criteria.

Radiation Planning and Treatment

Planning Computed Tomography (CT)

Planning CT (Somatom Plus 4, Siemens, Erlangen, Germany) was performed with 2 mm slice thickness and no interslice gap throughout the whole sequentially acquired region of interest, with the patient immobilized in a commercially available thermoplastic mask including head and shoulder region, and with an integrated individually customized bite block.

Planning systems: Contouring and plan optimization were performed on a Varian Treatment Planning System (Eclipse®, Version 7.3.10, Varian Medical System, Hansen Way, Palo Alto, CA, USA.

Delineation of Planning Target Volumes (PTVs)

Definitions:

- GTV = gross tumor volume;
- CTV = clinical target volume for elective lymph nodes (volume definitions according to the recommendations of Gregoire et al. [9]);
- PTV = planning target volume;
- PTV1 = GTV plus 10–15 mm;
- PTV2 = CTV plus 5–10 mm for doses between 48–56 Gy.

Dose Constraints for Normal Tissues/Organs at Risk (OARs)

Irradiation planning aimed at target doses of 60–70 Gy respecting the tolerance limits as follows:

- spinal cord: $D_{max} < 45$ Gy , $D_{mean} < 35$ Gy (spinal cord was contoured at least with a 5- to 10-mm margin, usually > 10 mm at the ventral aspect);
- parotid (entire or partial) gland volume, spared to the degree possible without compromising target coverage: $D_{mean} \leq 26$ Gy;
- temporomandibular joint (TMJ): $D_{max} < 50$ Gy;
- brain: $D_{max} < 40$ Gy;
- oral cavity outside the PTV: $D_{mean} < 35$ Gy, contouring of the oral cavity also included the mandibular and maxillary bone and the oral vestibule;
- nuchal tissue: $D_{mean} < 45$ Gy.

In order to obtain complete dose-volume histograms (DVHs) for the recent analysis, the entire mandible volume was retrospectively contoured in each patient.

Radiation

Irradiation was delivered by 6-MeV photon beams on a Varian linear accelerator with sliding window MLC (multileaf collimator) technique. Technical solution resulted in five-field arrangements ("class solution") for most patients (n = 61), six fields were applied in five, seven fields in seven patients.

In all patients, SIB-IMRT technique was performed using the following schedules:

- 30 × 2.2/1.8 Gy to 66 Gy (PTV1)/54 Gy (PTV2; n = 28);
- 33 × 2.11/1.64 Gy to 69.6 Gy/54 Gy (n = 25);
- 30 × 2.11/1.8 Gy to 63.3/54 Gy (n = 3);
- 30–35 × 2.0 Gy to 60–70 Gy (n = 16 postoperative patients).

In one case with large necrotic nodes, a higher SIB dose of 2.35 Gy per fraction to 75.2 Gy to the nodal GTV was chosen.

PTV homogeneity was aimed to be in accordance with the RTOG guidelines:

- the prescription dose is the isodose which encompasses at least 95% of the PTV;
- no more than 20% of any PTV will receive > 110% of its prescribed dose;
- no more than 1% of any PTV will receive < 93% of its prescribed dose;
- no more than 1% or 1 cm^3 of the tissue outside the PTV will receive > 110% of the dose prescribed to the primary PTV.

Dental Care Prior to Radiation Therapy

All patients were seen in the Outpatient Clinic of the Department of Oral and Maxillofacial Surgery. Dental treatment following Daly's guidelines was performed [3]. Patients were provided with an individual fluoride carrier and were instructed in dental care. During the RT course these patients had one to two appointments for oral hygiene.

Amifostine or saliva substitutes were not used [15, 16].

Methods

DVHs of the whole mandibular bone were obtained by contouring the entire mandible in each patient's planning CT. DVHs were analyzed with respect to volumes (cm^3) and percentage of volume of the mandible. Data were related to the observed mandibular bone tolerance. In 63/73 cases complete dosimetric and volumetric data were available; of the remaining ten data sets, two were not evaluable due to mandibular resection prior to irradiation, and eight

Table 1. Doses delivered to partial volumes (in cm^3) of the mandibular bone. Note that in nine patients with a mean tumor dose of 64.8 Gy, < 60 Gy was delivered to the mandibular bone.

Tabelle 1. Volumina (in cm^3) der mit den angegebenen Dosen bestrahlten Kieferknochen. Anzumerken ist, dass bei neun Patienten mit einer mittleren Tumordosis von 64,8 Gy der Kieferknochen mit < 60 Gy belastet wurde.

	< 60 Gy	> 60 Gy	> 65 Gy	> 70 Gy	> 75 Gy
Mandibles (n)	9	52	48	27	6
Mean volume (cm^3)		7.8	4.8	0.9	0.29
Range (cm^3)		0.3–23.7	0.1–16.8	0.1–6.0	0.1–0.75

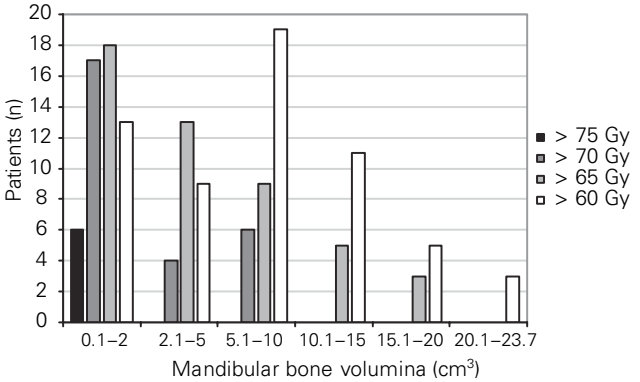

Figure 1. Dose-volume histogram-(DVH-)based bone volumes (in cm^3) of 54/63 mandibles exposed to IMRT doses > 60, > 65, > 70, and > 75 Gy, respectively. In nine cases, doses to the mandible could be kept < 60 Gy (in seven of these nine patients, the tumor dose was > 66 Gy [range 60–69.6 Gy]).

Abbildung 1. Dosis-Volumen-Histogramm-(DVH-)basierte Kiefervolumina von 54 der 63 analysierten Kieferknochen: Dargestellt sind Volumina, die Dosen > 60, > 65, > 70 und > 75 Gy ausgesetzt waren. Bei neun Patienten konnte die Kieferdosis < 60 Gy gehalten werden (bei Tumordosen > 66 Gy [60–69,6 Gy] in sieben der neun Fälle).

were lost due to a malfunctioning electronic transfer from the data bank.

Results

Dosimetry of the Mandible

The mean mandibular volume was 58.4 cm^3, ranging between 33 and 88 cm^3, mean GTV measured 31.6 cm^3 (range 2–132 cm^3), and the mean SIB volume (PTV1) was 164 cm^3 (range 31–393 cm^3), respectively.

In 42 patients a mean mandible volume of 4.6% (range 0.5–15%) received > 100% of the PTD. Only 16 of those 42 mandibles were exposed to doses > 105% (mean 1.7%, range 0.1–4% of the bone volume). Mean D_{max} in all patients was 71.0 Gy (range 59.6–80 Gy), and mean D_{mean} 38.3 Gy (range 17.9–56 Gy).

Absolute doses delivered to partial volumes of the mandibular bone (in cm^3) are shown in Table 1. In Figure 1, absolute bone volumes exposed to doses > 60, 65, 70, and 75 Gy are analyzed.

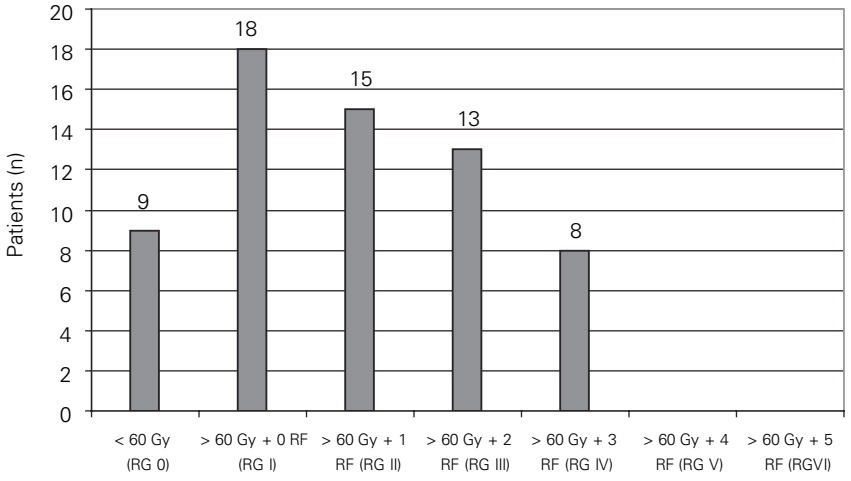

Figure 2. Distribution of various risk factors (RF) for ON in 63 IMRT patients. Risk groups (RG) 0–VI were defined as follows: patients with doses < 60 Gy to the mandible were classified as RG 0; patients with mandible bone doses > 60 Gy as the only risk factor were defined as RG I; patients with mandible doses of > 60 Gy plus one of the following RFs were classified as RG II, and with all five following as RG VI, respectively:
- bone infiltration (n = 1),
- macroscopic tumor-to-bone distance of < 4 mm (n = 33),
- ≥ 95% of the SIB delivered to the entire bone diameter to a length of 5–30 mm (n = 16),
- teeth in the high-dose area (n = 8),
- ≥ 2 cm^3 of the bone exposed to ≥ 70 Gy (n = 5).

Abbildung 2. ON-Risikofaktoren (RF) bei 63 Patienten. Es wurden Risikogruppen (RG) 0–VI zur Abschätzung des ON-Risikos bei IMRT-Patienten gebildet. Patienten mit Kieferdosen < 60 Gy wurden der RG 0 zugeordnet, bei Kieferbelastung > 60 Gy der RG I; pro zusätzlichen Risikofaktor Zuordnung zur nächsthöheren RG bis hin zu RG VI bei Vorliegen aller folgenden fünf Risikofaktoren zusätzlich zu einer Exposition von > 60 Gy:
- Knocheninfiltration (n = 1).
- makroskopische Tumordistanz zum Knochen von < 4 mm (n = 33),
- ≥ 95% des Boostvolumens auf einer Länge von 5–30 mm auf den gesamten Knochendurchmesser appliziert (n = 16),
- Zähne in der Knochenregion mit hoher Dosis (n = 8),
- ≥ 2 cm^3 des Knochenvolumens einer Dosis ≥ 70 Gy ausgesetzt (n = 5).

Figure 2 shows the risk profile of the cohort. Patients were grouped according to five risk factors in addition to a mandible dose > 60 Gy.

In 9/63 cases (15%) doses to the mandible were < 60 Gy and therefore bone was not at risk.

Mandibular Bone Tolerance

Only a single patient with a radiation-associated bone event has been observed, following SIB-IMRT with 30 × 2.2 Gy to a total dose of 66 Gy for a T3 N2b base of tongue carcinoma. Grade 3 ON (bone necrosis of the exposed superficial cortical bone, needing decortication of the lingual corticalis) occurred 6 months after IMRT completion, and was surgically completely resolved by a transoral local bone decortication. Mean and maximum mandibular doses were 42 Gy and 74 Gy, respectively. A small bone volume of 0.36 cm^3 received > 65 Gy, only 0.18 cm^3 > 70 Gy (106% of prescribed dose), however, there was a hot spot of 115% delivered to the adjacent mucosal tissue of the ipsilateral floor of mouth as a theoretical source of tissue damage. No teeth were in the high-dose area, and no SIB dose was delivered to the corresponding buccal cortex, classifying this patient for risk group 1 (Figure 2).

Locoregional Control

Locoregional tumor control was achieved in 59/73 patients (~ 80%) after a mean overall observation time of 22 months (12–46 months). 3/12 patients with locoregional failure also had distant metastases. When local control was analyzed according to the tumor entity, 9/18 oral cavity tumors (50%), and 3/55 oropharyngeal tumors (~ 5%) failed.

Discussion

This is the first report on relative and absolute dose-volume relationships in IMRT-spared mandibular bone.

Dosimetric data published on irradiated mandible bone volumes are sparse.

Jereczek-Fossa et al. measured dose distributions of the mandible in 18 oropharyngeal cancer patients treated with bifractionated 3D-CRT (62 × 1.2 Gy bid to 74.4 Gy) [13]. Those authors found a mean of 28.6% (range 10.2–58.1%) of the mandibular volume was exposed to doses higher than the PTD, mainly in the molar and retromolar region of the horizontal branch. The authors measured a mean mandibular volume of 82.3 cm^3 (range 60.1–110.1 cm^3); mean cumulative DVH-

based volumes exposed to at least 10%, 20%, 50%, 80%, and 100% of the PTD were approximately 90%, 85%, 75%, 50%, and 20% of the mandible (Figure 3 in [13], page 53). In nine patients (50%), 50% of the mandible received > 88% of the PTD. The analysis by Jereczek-Fossa et al. represents a careful dosimetric evaluation of conformal 3D-CRT as it was also a standard schedule in our institution before IMRT implementation, and therefore these data were useful for comparative purposes with the dosimetric IMRT data presented in the current study. This comparison reveals an approximate reduction of mandibular volume exposed to high-dose IMRT of ~ 15%, 35%, and 17% at doses of > 50%, 80%, and 100% of PTD, respectively (Figure 3).

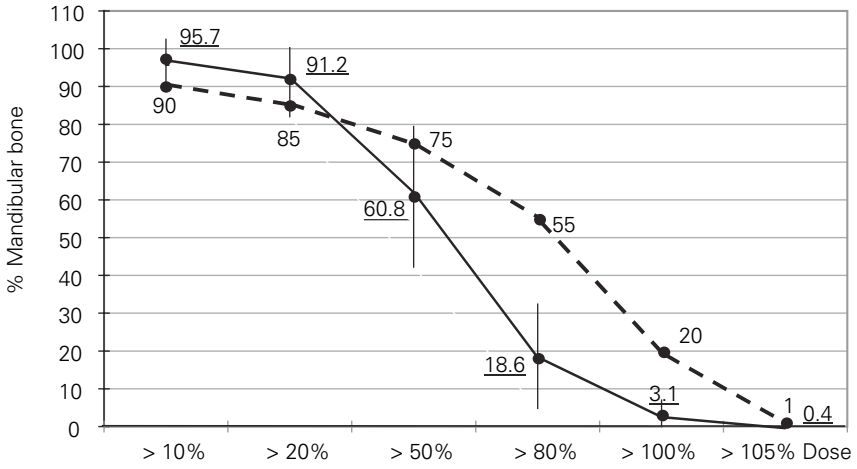

Figure 3. Dose-volume histograms (DVHs) in 63 patients with complete dosimetric and volumetric data. Mean cumulative IMRT DVH (with standard deviations) compared to the mean cumulative 3D-CRT DVH (bold values, dotted line) from 18 patients analyzed by Jereczek-Fossa et al. [13]: an approximate reduction of 15%, 35%, and 17% of mandibular volumes exposed to > 50%, > 80%, and > 100% of prescribed doses was achieved with IMRT technique.

Abbildung 3. Mittelwerte der Dosis-Volumen-Histogramme (DVHs) von 63 Patienten, deren dosimetrische und volumetrische Daten vollständig vorlagen. Mittleres kumulatives IMRT-DVH (mit Standardabweichungen) im Vergleich zum mittleren kumulativen DVH von 18 konventionell bifraktioniert bestrahlten Patienten (fette Zahlen, gestrichelte Linie) in der Analyse von Jereczek-Fossa et al. [13]: Für die IMRT-bestrahlten Kiefer zeigt sich eine mittlere Reduktion von 15%, 35% und 17% des Knochenvolumens, das Dosen von > 50%, > 80% und > 100% der Herddosis ausgesetzt war.

Intraindividual dose-volume comparisons between 3D-CRT and IMRT plans in two patients (one with oropharyngeal and one with nasopharyngeal cancer) are reported by Parliament et al. [18]. However, mandible bone contouring and dose-volume constraining were not specifically performed to spare mandible bone in the IMRT cases and therefore these results are of limited comparative value.

In our patients very small partial volumes of the mandibular bone were exposed to high doses. This was achieved by contouring and defining dose-volume constraints for the mandibular bone outside the PTV. Dose maxima were "point doses" to at least one image voxel; such "hot spots" may blur with minimal daily position deviations and therefore they do not necessarily reflect true local overdosage. We found that the highest dose delivered to the bone was at the lingual cortex close to the PTV1, with steep dose gradients toward the buccal mandibular cortex in most cases. In 16/63 mandibles, high dose encompassed the entire bone diameter across the horizontal branch. The observation of high doses mainly delivered to the lingual cortex with IMRT may, theoretically, additionally reduce the risk of ON, when considering the report by Bras et al., hypothesizing the buccal cortex to be at the

Table 2. Published success rates of endosteal implants in irradiated and nonirradiated jaws from the last few years. An approximately 10% higher implant survival rate is reported for nonirradiated mandibles compared to jaws irradiated with doses exceeding ~ 50 Gy. FU time: follow-up time; RT: radiotherapy.

Tabelle 2. Publizierte Erfolgsraten der letzten Jahre für Zahnimplantate in bestrahlten und nichtbestrahlten Kiefern. Es wird ein Implantatüberlebensvorteil von ca. 10% für nichtbestrahlte Unterkiefer gegenüber Kieferknochen nach ~ 50 Gy überschreitenden Strahlendosen festgestellt. FU time: Beobachtungszeit; RT: Radiotherapie.

Authors (year)	RT	Patients (n)	Mandible implants (n)	Implant success rate (%)	FU time (years)	Recruitment interval
Granstrom et al. (2005) [8]	Yes	107	471	75	6.3	1979–2003
Visch et al. (2002) [21]	Yes	130	446	85	10	1987–2001
Grotz et al. (1999) [11]	Yes	47	111	72	5	1988–1997
Esser & Wagner (1997) [6]	Yes	60	221	80	5	1985–1995
Weischer & Mohr (1999) [22]	Yes	18	83	75/86	7	1988–1991/1992–1997
Weischer & Mohr (1999) [22]	No	22	92	86/94	7	1988–1991/1992–1997
Haas et al. (1996) [12]	No	714	1 920	90	8.3	1984–1993
Noack et al. (1999) [17]	No	883	1 964	94	5	1981–1997

highest risk [2]. Also in patients with a PTV abutting the mandible, the high dose often did not extend over the whole cross section.

This dose reduction translated into a very low ON incidence of one case in 73 patients. In a recently published analysis of 50 patients treated with IMRT for oropharyngeal cancer between 1998 and 2004, one patient was suspected to have an ON in an area measuring 5 mm of exposed bone, where 70 Gy were delivered. However, radiologic investigations and further physical examination did not confirm this finding, and that patient underwent successful conservative treatment [4].

Selection of patients "at risk" for ON was performed according to the historical 3D-CRT criteria, however, with IMRT several of them (15% of the cohort) are no longer "at risk", due to doses < 60 Gy delivered to bone. In consequence, an IMRT-adapted ON risk factor score is proposed aiming at a more accurate ON risk estimation in IMRT patients (Figure 2). The observation time is too short to assess the value of this scoring system. As only one event happened in our cohort, further prospective evaluation is ongoing to assess the significance of this intuitively defined risk group system.

Mandible and soft-tissue conditions are very important in postirradiation dental implant and reconstructive procedures. Table 2 gives an overview of reported endosteal implant success rates in the last few years [6, 8, 11, 12, 17, 21, 22]. These data indicate the relevance of bone and adjacent soft-tissue irradiation to dental and reconstructive management.

Based on the presented clinical and dosimetric results, the ON incidence rate is expected to decrease from approximately five events in 100 treated patients (5%) to one to two (1–2%). Apart from a substantial gain in terms of quality of life [14, 23], generally reduced early and late side effects, and a likely improved tumor control, there is also an advantage in terms of cost benefit. When the cost for a single incident of grade 3 ON is estimated to be 30,000–40,000 Euros, a substantial amount of the additional costs for IMRT treatment would be covered.

The documented mandibular protection with IMRT may therefore translate into (1) a further reduction of the incidence of ON, and (2) a better outcome of osseointegration of implants and posttreatment reconstructive procedures.

Conclusion

IMRT permits high-dose irradiation of oropharyngeal and oral cavity tumors with good locoregional control, yet with very small partial volumes of the mandibular bone exposed to high doses. This is expected to translate into a further reduction of the risk of ON and an improved outcome of osseoimplantation in irradiated patients. Longer follow-up and larger sample sizes are needed to confirm the reduction in the risk of mandibular ON following IMRT.

Early outcome analysis of endosteal implant survival in our IMRT cohort is in preparation.

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